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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,623	08/27/2001	Xianxhang Yu	035879-0125	2349

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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/938,623	YU ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-11,13-32,34-50 and 52-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-6, 8-11, 13, 14, 21-27, 29-32, 34, 35, 40-45, 47-50, 52, 53, 58-60* is/are rejected.

7)☐ Claim(s) *7, 15-20, 28, 36-39, 46 and 54-57* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20070726*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

After review and reconsideration, the finality of the Office action of July 18, 2006, is withdrawn, and the Office action of mailed Feburary 7, 2007 is vacated for the reasons set forth in the accompanying interview summary.

Claims 1-11, 13-32, 34-50 and 52-60 are pending an under consideration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 58 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "target cell" in claim 58 lacks proper antecedent basis in claim 40.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 8, 13, 14, 21-24, 26, 29, 34, 35, 40-42, 44, 47, 52, 53, 58-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Rivett et al (WO 97/33908, IDS reference).

Claim 1 is drawn to a procytotoxin comprising a cytotoxic peptide bound to an inactivator via a peptide bond, wherein said cytotoxic peptide is a pore-forming cytolytic peptide that comprises an amphipathic alpha-helical structure, and wherein said peptide bond is susceptible to cleavage by a targeting specific protease. Claim 2 embodies the procytotoxin of claim 1 wherein the inactivator is selected from a group including a peptide. Claim 3 embodies the procytotoxin of claim 1 wherein said inactivator is added to the C-terminus. Claim 5 specifies that the specific protease is PSA. Claim 8 requires a further targeting molecule. Claim 13 embodies the procytotoxin of claim 1, wherein said cytolytic peptide is selected from a group

including magainin and melittin. Claim 14 specifies melittin. Claim 21 is drawn to a pharmaceutical composition comprising the procytotoxin of claim 1 and a suitably acceptable carrier or excipient.

Claim 22 is drawn to a method for selectively destroying a target cell comprising contacting said cell with a procytotoxin which comprises a cytotoxic peptide bound via a peptide bond to an inactivator, wherein said cytotoxic peptide is a pore-forming cytolytic peptide that comprises an amphipathic alpha-helical structure, and wherein the peptide is susceptible to cleavage by a specific protease. Claim 23 embodies the method of claim 22 wherein said inactivator is selected from a group including a peptide. Claim 24 embodies the method of claim 22 wherein said inactivator is added to the C-terminus. Claim 26 embodies the method of claim 22 wherein the specific protease is PSA. Claim 29 embodies the method of claim 22 wherein said procytotoxin further comprises a targeting molecule. Claim 34 embodies the method of claim 22, wherein said cytolytic peptide is selected from a group including magainin and melittin. Claim 35 specifies melittin. Claim 21 is drawn to a method of treating cancer patients comprising the administration of the pharmaceutical composition of claim 21.

Claim 40 is drawn to a method of making a procytotoxin comprising modifying a cytolytic peptide to include an inactivator, wherein said cytotoxic peptide is a pore-forming cytolytic peptide that comprises an alpha-helical pore-forming structure. Claim 41 embodies the method of claim 40 wherein said inactivator is selected from a group including a peptide. Claim 44 embodies the method of claim 40 wherein the specific protease is PSA. Claim 47 embodies the method of claim 40 wherein the procytotoxin further comprises a targeting molecule. Claim 52 embodies the method of claim 40,, wherein said cytolytic peptide is selected from a group including magainin and melittin. Claim 53 specifies melittin. Claim 58 embodies the method of claim 40 wherein the target cell is a cancer cell. Claim 59 specifies that said cancer cell is selected from a group encoding prostate.

Rivett et al disclose a procytotoxin comprising lytic peptide bound to an inactivator via a peptide bond, wherein said cytotoxic peptide comprises an amphipathic alpha-helical structure, and wherein said peptide bond is susceptible to cleavage by a targeting specific protease, including PSA (page 4, lines 24-31, page 29, line 27 to page 30, line 6). Rivett et al disclose that magainin and melettin are cytotoxic peptide having an alpha helical structure (page 1 lines 20-

24, and lines 27-28 and page 1, line 33 to page 2, line 23). Rivett et al disclose the treatment of cancer, specifically prostate carcinoma, by the administration of such procytotoxins (page 3, line 36 to page 5, line 1 and page 13, line 3). Rivett et al disclose a cleavable moiety located carboxyl terminal to said helix (page 13, lines 15-20). Rivett et al disclose that the cleavable moiety may be any moiety which can be linked to the alpha helix causing inactivation of lytic function, and that preferable the cleavable sequence is selectively removable by enzymatic means including PSA (page 13, lines 21-26). Rivett disclose targeting moieties for the procytotoxin, such as scFv (page 32, Ex 7, page 4, line 36 and page 12, lines 26-37). Rivett et al disclose attachment through the N-terminus and the C-terminus (abstract, page 4, lines 24-29, page 30, lines 33-35).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8-10, 13, 14, 21-27, 29-31, 34, 35, 40-45, 47-49 and 52, 53, 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rivett et al (WO 97/33908) in view of Glazier (U.S. 2003/0138432, cited in a previous Office action), Thorpe et al (U.S. 6,342,219) and Rawlings et al (Biochimica et Biophysica Acta, 1997, Vol. 1339, pp. 247-252).

Claim 4 embodies the procytotoxin of claim 1 wherein the specific protease is a matrix metalloproteinase. Claim 25 embodies the method of claim 22 wherein said specific proteinase is a MMP.

Rivett et al teaches the procytotoxin having an inactivating moiety comprising a peptide which is cleavable by PSA for the reasons set forth above. Rivett et al suggests that many other presequences are possible requiring only a cleavage site which is not present in the main peptide chain (page 30, lines 4-6). Rivett et al do not specifically teach a presequence which is cleavable by MMP.

Glazier teaches the targeting specific proteases of PSA (paragraphs 1329, 1354-1356), PSMA (paragraphs 710, 1015, 1019) and matrix metalloproteinases (paragraphs 0698, 699 and 727-732). Glazier teaches the targeting of tumor neovasculature for drug delivery (paragraphs 958, 1291) and the use of the "RGD" targeting sequence (paragraphs 954-955).

Thorpe et al teach "biologically-releasable bonds" including cleavable spacer or linker which can be cleaved by MMP (column 92, lines 8-30 and Table 2B). Thorpe et al teach the use of peptide linkers that include a first cleavage site for a peptidases or proteinase that preferentially located with in a disease site, preferable within the tumor environment results in the specific release of active agent in the vicinity of a tumor (column 92, line 61 to column 93, line 31).

Rawlings et al teach that PSMA is an endopeptidase capable of cleaving internal bonds in poly-gamma-glutamate chains (page 247, second column, lines 12-17 and page 249, first column, lines 13-20).

It would have been prima facie obvious at the time the invention was made to incorporate a presequence cleavable by MMP, such as that taught by Thorpe et al and direct the procytotoxin of the invention to the neovasculature surrounding a tumor cell by means of the "RGD" peptide sequence to allow for a larger targeting area. One of skill in the art would have been motivated to do so by the teachings of Glazier on the "RGD" tumor neovasculature targeting sequence, and the targeting to specific proteases, such as the MMP protease and the teachings of Thorpe et al on the release of an active agent fused to the MMP cleavable peptide within the tumor microenvironment. It would also have been obvious to target the specific protease of PSMA as taught by Glazier by relying on the endopeptidase activity of PSMA as taught by Rawlings. One

of skill in the art would have been motivated to do this because PSMA is a cell surface prostate cancer associated antigen and thus the endopeptidase activity and release of the cytotoxin would be localized to the tumor microenvironment.

Claims 1-3, 5, 8, 9, 11, 13, 14, 21-24, 26, 29, 30, 32, 34, 35, 40, 42, 44, 47, 48, 50, and 52, 53, 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rivett et al (WO 97/33908) in view of Neri et al (WO 97/45544, provided in the Office action mailed February 7, 2007).

Neri et al teach the in vivo targeting of tumor vasculature comprising the administration of recombinant anti-fibronectin ED-B antibodies (page 1, lines 4-9, page 22-27, examples 1 and 2 and page 35, example 3). Neri et al teach that targeting of the tumor vasculature is an indirect form of tumor therapy resulting in the damaging of the blood vessels supplying the tumor (page 16, lines 13-26).

It would have been prima face obvious to use the targeting sequence of the recombinant anti-fibronectin taught by Neri et al in the method of Rivett et al. One of skill in the art would have been motivated to do so by the teachings of Neri et al on the ability to damage tumor vasculature as a means of tumor therapy.

The provisional rejection of claims 1, 2, 4-10, 13-23, 25-31, 34-39 and 60 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 09/851,422 in view of Glazier (U.S. 2003/0138432) is withdrawn in light of applicant's Terminal Disclaimer

The provisional rejection of claims 1, 2, 7, 13-15, 17, 18, 20-23, 28, 34-36 and 38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of copending Application No. 11/131,443 is withdrawn because 11/131,443 is the later filed application. It is noted that applicant has submitted two terminal disclaimers on January 11, 2007; however, only the Disclaimer relating to 09/815,422 has been processed and approved. Applicant has only been charged a single fee for the Statutory Disclaimer.

Claims 7, 15-20, 28, 36-39, 46 and 54-57 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A. Canella/
Ph.D., Primary Examiner,
Art Unit 1643